DANISH MEDICAL BULLETIN

A SURVEY OF DANISH MEDICINE

PUBLISHED BY

UGESKRIFT FOR LÆGER

THE MEDICAL FACULTIES OF THE UNIVERSITIES OF COPENHAGEN AND AARHUS

THE NATIONAL HEALTH SERVICE OF DENMARK

CONTENTS

Subscription: Ejnar Munksgaard, 6, Norregade, Copenhagen, Denmark

Price: In Scandinavia Dan. Crowns 15.00, in Europe £ 1/-/-, Outside Europe $ 3.00 or Equivalent

Free of Charge for Medical Institutions on Request

VOL 1
DECEMBER 1954

A Publication of
THE DANISH MEDICAL ASSOCIATION
Domus Medica, Copenhagen Ø, Denmark

NO 7
PAGES 189-216

VOL 1 NO 7 **DANISH MEDICAL BULLETIN** DECBR. 1954

GENETIC CAUSAL FACTORS IN CANCER OF THE STOMACH

By AAGE VIDEBÆK and JOHANNES MOSBECH

Our knowledge of the etiology of cancer of the stomach, as of the majority of other types of cancer, is limited. Fibiger (5) was the first to produce cancer of the stomach experimentally. As demonstrated later, this form of cancer in rats is probably not solely ascribable to the nematode found by Fibiger (15). Later, cancer of the stomach was produced also in mice by injecting carcinogenic hydrocarbon into the stomach wall or subcutaneously or by adding carcinogenic hydrocarbon to the animals' food (10). Strong possesses a strain of mice which shows a high incidence of so-called spontaneous cancer of the stomach which, on experimental breeding, has proved to be determined by hereditary factors (16).

The incentive to investigate whether hereditary factors are of significance in the development of cancer of the stomach in man originates partly from Strong's observations concerning a hereditary conditioned cancer of the stomach in mice and partly from the knowledge that human cancer of the stomach is so common and has such a poor prognosis that considerable endeavours are justified even although the result of such an investigation be perhaps slight or negative.

In the present investigation, the so-called proband method was employed. This method is extremely time-consuming and requires comprehensive correspondance and patience both in the relatives concerned and in the investigator. Provided this patience is present, far reaching results may be obtained, at any rate in Denmark where the information necessary for such an investigation is available to a great extent even from a remote time. The investigation could be carried out relatively easily thanks to the invaluable help for the performance of the task rendered by physicians and hospitals, particularly all the hospitals in Copenhagen.

From The Institute of Genetics, Copenhagen University. Head: Prof. *T. Kemp.*

With financial assistance from The National Cancer Institute of The National Institutes of Health, U. S. Public Health Service.

PATIENT MATERIAL

The investigation comprized the children, siblings, parents and, in several cases, also siblings of parents of a total of 302 probands with verified cancer of the stomach. 3,294 relatives, i. e. on an average 11 relatives per proband, are concerned.

The information collected was confirmed as appears from Table 1.

Table 1.
Investigation of the Relatives of 302 Patients and 390 Controls.

	Patient material	Control material
Alive, no cancer	1,668 (51 %)	1,762 (36 %)
Cancer	366 (11 %)	346 (7 %)
verified in hospital ..	230	192
verified by death certificate	132	127
Dead, no cancer	1,260 (38 %)	2,674 (56 %)
case-history controlled	36	78
death certificate controlled	799	1,004
died under 10 years of age.....	109	185
died from tuberculosis, suicide or accident....	116	165
	3,294	4,782

Table 2.
Incidence of Cancer of the Stomach in Patient Material and Control Material.

	Patient material	Control material
No. families with 0 case of cancer of the stomach	196 (65 %)	339 (87 %)
» » » 1 case » » » » »	76 (25 %)	44 (11 %)
» » » 2 cases » » » » »	19 (6 %)	7 (2 %)
» » » 3 cases » » » » »	9 (3 %)	0
» » » 4 cases » » » » »	2 (1 %)	0

The diagnoses in the probands were verified in 79 per cent. by microscopic examination, in another 12 per cent. by exploratory laparotomy, in 8 per cent. by autopsy without microscopic examination and in 1 per cent. only by gastroscopy and typical radiological findings. It was further ascertained that the 302 probands were representative of cancer of the stomach in respect of age, sex distribution and site of the tumour in the stomach.

CONTROL MATERIAL

This consists of 390 probands with 4,782 relatives, i. e. on an average 12 relatives per proband.

The probands were symptom-free individuals. 17 per cent. were old age pensioners in »The Old Folk's Town« (»De Gamles By«), 38 per cent. were old age pensioners outside »The Old Folk's Town«, 19 per cent. were employees in the machine factory »Titan« and the drug factory »Novo«, 14 per cent. friends and acquaintances and 12 per cent. hospital employees.

The control material was investigated in view of the occurrence of cancer, the same technique being employed as in the patient material. The information collected was confirmed as appears from Table 1.

As the age distribution is of great significance when the incidence of cancer is evaluated, the control material must comprize individuals with the same age distribution as the relatives of the probands suffering from cancer of the stomach. Figure 1 shows that the age distribution of the relatives in the patient and control materials correspond to a great extent.

RESULTS

On analysis of the patient and control materials, many more cases of cancer of the stomach are encountered in the patient material than in the control material.

Table 2 shows that in the patient material considerably more families are afflicted with cancer of the stomach and that in the patient material several families are encountered in which 3 or 4 cases of cancer of the stomach occur.

Table 3 shows preponderance of the incidence of cancer of the stomach in each separate group of relatives in the patient material where the incidence is approximately 4 times that in the control material.

Table 4 shows that the incidence of all forms of cancer other than in the stomach is more or less the same in the two materials.

In Table 5, the number of cases of cancer, in the stomach or elsewhere, among the relatives has been tabulated. It appears, that cancer of the stomach comprizes over 40 per cent. of all cancer in the relatives in the patient material while in the control material cancer of the stomach com-

Table 3.
Cancer of the Stomach in Patient Material and Control Material.

	Patient material.			Control material.		
	No. of relatives	Cases of cancer of the stomach	Cancer of the stomach. Incidence (%)	No. of relatives	Cases of cancer of the stomach	Cancer of the stomach. Incidence (%)
Fathers	284	36	12½	390	8	2
Brothers	731	33	4½	931	8	1
Fathers' brothers	179	8	4½	301	6	2
Mothers' brothers	122	5	4	329	10	3
Sons	352	2		474	2	
Total males	1,662	84	5.0	2,425	34	1.4
Mothers	284	25	9	390	8	2
Sisters	684	22	3	897	4	½
Fathers' sisters	169	9	5½	263	7	3
Mothers' sisters	147	8	5½	349	5	1½
Daughters	342	1		458	0	
Total females	1,626	65	4.0	2,357	24	1.0

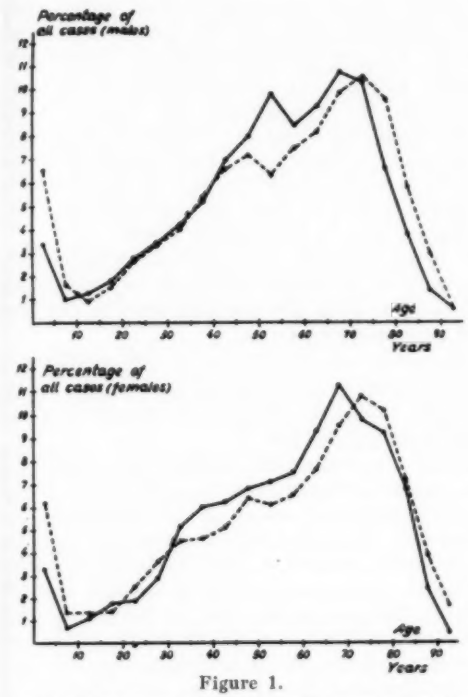


Figure 1.

Age Distribution of All Male and Female Relatives in the Patient Material (————) Compared with the Age Distribution of All Male and Female Relatives in the Control Material (- - - - - -).

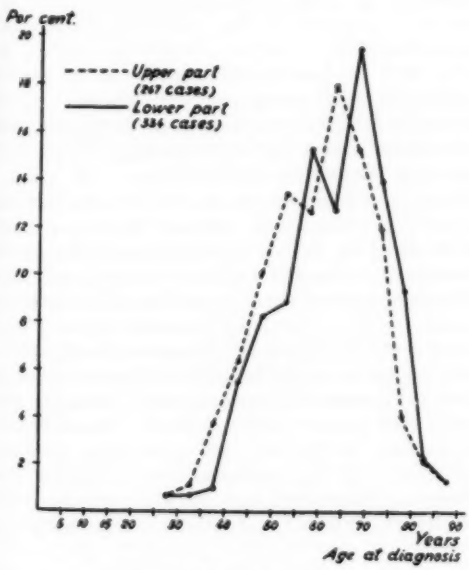


Figure 2.

Age Distribution of Patients With Cancer in the Body or the Fundus of the Stomach Compared With the Age Distribution of Patients With Cancers in the Pyloric Antrum or Pyloric Canal.

Table 4.

Incidence of Extra-Gastric Cancer in Patient Material and Control Material.

	Patient material		Control material	
	No. patients	Cancer incidence (%)	No. patients	Cancer incidence (%)
Fathers	34	12	39	10
Brothers	38	5	52	5½
Fathers' brothers.	20	11	15	5
Mothers' brothers.	5	4	19	6
Sons	4			
Total males.....	101	6.1	128	5.2
Mothers	37	13	38	10
Sisters	49	7	61	7
Fathers' sisters ..	18	10	24	9
Mothers' sisters ..	11	7	33	9
Daughters	1			
Total females ...	116	7.1	160	6.8

Table 5.

Cancer of the Stomach and in Other Sites in Patient Material and Control Material.

	Patient material		Control material	
	No. patients	% of all cancers	No. patients	% of all cancers
Stomach	149	41	58	17
Other sites ..	217	59	288	83
Total	366	100	346	100

prizes only 17 per cent. of all the cases of cancer registered.

The average age for probands with cancer of the stomach, situated in the body or the fundus of the stomach is significantly lower both for males (58.2 years) and females (59.0 years) than for probands in whom the tumour was situated in the pyloric antrum or pyloric canal where the average ages are 60.7 and 64.8 years respectively.

In agreement with this, Figure 2 shows that the curve for age distribution for patients with cancer of the body of the stomach or the fundus is displaced to the left and that the curves intersect at a point corresponding to the age of 65 years. It thus appears as if cancer of the fundus develops earlier than do tumours adjacent to the pylorus. This is perhaps due to different pathogenesis in the two groups.

Affliction with cancer of the stomach among the relatives is slightly greater in those cases in which the tumour in the proband is situated in the upper part of the stomach, but the difference is, however, not significant.

Table 6 shows the risk of developing cancer of the stomach in the nearest relatives of patients with cancer of the stomach as compared with the risk of developing cancer of the stomach in the nearest relatives of the control material, calculated by M. Nyholm (7). (By »cancer risk« is

Table 6.

Risk of Developing Cancer of the Stomach in Relatives of Patients and Controls.

	Patient material	Control material
Fathers	34 %	6 %
Brothers	35 %	6 %
Fathers' brothers	16 %	6 %
Mothers' brothers	14 %	10 %
Total males	29 %	7 %
Mothers	23 %	6 %
Sisters	22 %	
Fathers' sisters ..	18 %	8 %
Mothers' sisters ..	18 %	4 %
Total females	21 %	5 %

understood the risk that the relatives concerned should develop cancer were they to survive until the age of 90 years). As might be anticipated from the preceding, it appears that while the risk of developing cancer of the stomach is only 5—7 per cent. in the control material, it is approximately 4 times as large for the nearest relatives of patients with cancer of the stomach, i. g. for brothers of patients with cancer of the stomach the risk of developing cancer of the stomach is 35 per cent. while for sisters the risk is 22 per cent.

Space does not permit us to explain here why it is inadvisable to draw any conclusions from these risk percentages concerning the heredity of the supposed cancer gene.

DISCUSSION

Evaluation of the data thus registered is difficult.

A pronounced familial incidence of cancer of the stomach similarly to the observations made concerning cancer of the breast (8), cancer of the body of the uterus (2) and leucaemia (19) might indicate that cancer of the stomach depends upon a hereditary predisposition but even if cancer of the stomach be dependent on a congenital predisposition, cancer is not encountered at birth and exogenic conditions must at least play a great part for the manifestation of cancer of the stomach.

Particularly in experimental cancer research it has been suggested that external conditons may accelerate the development of cancer and that so-called carcinogenic substances act by accelerating the development of that tumour which the animals might develop spontaneously.

It is probable that the slightly higher incidence of cancer of the stomach in males depends upon the fact that males are more exposed to factors accelerating cancer of the stomach and when the incidence of cancer of the stomach increases greatly with advancing age, the explanation may be that time implies greater risk of encountering or of still being subjected to these accelerating factors, should they exist. We are, however, unable to demonstrate such external carcinogenic factors. Achylia (4) is considered to be significant for the development of cancer of the stomach but only about 60 per cent. of the patients with cancer of the stomach have achylia (17) and achylia is on the whole frequent in individuals in those age groups in which the incidence of cancer of the stomach is particularly great.

It is, however, also presumed that achylia plays a part in the formation of polypi in the stomach (4) and polypi of the stomach must be regarded as a precancerous change.

The study by McNeer of 500 particularly young patients suffering from cancer of the stomach (12) has emphazised the patho-genetic significance of achylia.

There is considerable evidence that cancers in the upper alimentary tract, particularly cancer of the tongue and cancer of the oesophagus, are dependent to a great extent on or are activated by external factors, as the incidence of cancer localized to the mouth and oesophagus is particularly high in occupations in which the consumption of alcohol is, on the whole, high. Such exogenic conditions are probably also the cause of the fact that the incidence of cancer of the upper alimentary tract is significantly higher in males than in females (6); for cancer of the oesophagus, the incidence is approximately 5 times and for cancer of the tongue approximately 6 times greater than in females. If the development of cancer of the stomach were significantly dependent on occupation or alcoholism, the incidence of cancer of the stomach would correspondingly be expected to be far higher in males than in females, but as far as is known the incidence of cancer of the stomach is not particularly high in certain occupations and the incidence of cancer of the stomach is only slightly higher in males than in females.

It must be regarded as proved that pernicious anaemia predisposes to cancer of the stomach particularly (9, 18) as in patients suffering from pernicious anaemia, the risk of developing cancer of the stomach is 3 times as great as in the average population (14). Pernicious anaemia per se, however, hardly predisposes to cancer of the stomach; more probably atrophic gastritis plays a part in the development of both pernicious anaemia and polypi and cancer of the stomach. The probable explanation of the fact that pernicious anaemia and cancer of the stomach have a familial incidence is, therefore, that achylia may be hereditarily conditioned and predispose to both diseases.

In confirmation of this, it has been demonstrated that among relatives of patients with pernicious anaemia, who always have achylia, not only an increased incidence of pernicious anaemia is found but that cancer of the stomach

occurs approximately 3 times as frequently among relatives of patients with pernicious anaemia as in an adequate control material (13).

We have therefore also investigated the incidence of pernicious anaemia among patients suffering from cancer of the stomach and among their relatives and found that per 10,000 individuals, 39 in the patient material and 21 in the control material suffered from pernicious anaemia, i. e. approximately twice as many relatives with pernicious anaemia in the patient material. The difference is, however, not significant.

According to the preceding account, it is scarcely probable that exogenic factors solely can be the causes of the greatly increased incidence of cancer of the stomach in relatives of patients with cancer of the stomach. The familial accumulation of cancer of the stomach must be presumed primarily to depend on a hereditary predisposition but various external factors may accelerate, while others possibly delay, the development of that cancer of the stomach to which the individual has inherited a predisposition. We do not know if the factor inherited is the tendency to develop atrophy of the gastric mucous membrane with secondary achylia or if it is the tendency to development of proliferation of the mucous membrane which may become malignant on account of exogenic factors. It appears, however, most probable that this defect, which seems to be hereditary, is localized to the gastric mucosa proper and that cancer of the stomach is an endogenic cancer in contrast to the so-called exogenic cancers, e. g. localized to the mouth, cervix of the uterus or skin in the development of which external conditions are thought to play the overwhelming part.

SUMMARY

The frequency of cancer of the stomach is, on an average, 4 times greater among the relatives of patients with gastric cancer than among controls while the incidence of cancer of other sites among the relatives of patients with gastric cancer is not significantly increased.

In the patient group, 41 % of all forms of cancer were cancers of the stomach, while in the control material the corresponding figures was 17 % only.

Cancer localized to the oral part of the stomach manifests itself on an average somewhat earlier than cancer localized to the antrum or the pyloric canal.

Hereditary disposition to cancer of the stomach seems to be present and exogenic factors are supposed to be able to accelerate the development of cancer of the stomach.

While among the male and female relatives of patients with cancer of the stomach, the risk of developing this diseases was found to be 29 % and 21 % respectively, the corresponding figures for the control material were calculated to 7 % and 5 % only.

References:

1) *Berkson, J., W. Walters, H. K. Gray & J. T. Priestley:* Proc. Staff Meet., Mayo Clin. 1952, *27:* 137—151.
2) *Brøbeck, O.:* Heredity in Cancer Uteri. Universitetsforlaget, Århus, 1949.
3) *Comfort, M. W., M. P. Kelsey & J. Berkson:* J. Nat. Cancer Inst. 1947, *7:* 367—373.
4) *Cromer, H. E., M. W. Comfort & H. R. Butt:* J. Nat. Cancer Inst. 1949, *10:* 497—503.
5) *Fibiger, J.:* Ztschr. Krebsforsch. 1913, *13:* 217—280.
6) *Harnett, W. L.:* A Survey of Cancer in London. Brit. Empire Cancer Campain 1952.
7) *Helweg-Larsen, H. F. & M. Nyholm:* To be published.
8) *Jacobsen, O.:* Heredity in Breast Cancer. Lewis & Co. Ltd. London, 1946.
9) *Kaplan, J. S. & L. G. Rigler:* Am. J. Med. Sci. 1945, *209:* 339—348.
10) *Lorenz, E. & H. L. Steward:* J. Nat. Cancer Inst. 1940, *1:* 273—276.
11) *Martin, L. & N. Lewis:* Lancet 1949, *257:* 1115—1120.
12) *McNeer, G.:* Am. J. Roentgenol. 1941, *45:* 537—550.
13) *Mosbech, J.:* Heredity in Pernicious Anemia. A Proband Study of the Heredity and the Relationship to Cancer of the Stomach. Munksgaard, Copenhagen, 1953.
14) *Mosbech, J. & Aa. Videbæk:* Brit. Med. J. 1950, *II:* 390—394.
15) *Passey, R. D., A. Leese & J. C. Knox:* J. Path. & Bact. 1935, *40:* 198—199.
16) *Strong, L. C.:* J. Nat. Cancer Inst. 1947, *7:* 305—308.
17) *Swynnerton, B. F. & S. C. Truelove:* Brit. Med. J. 1952, *1:* 287—292.
18) *Torgersen, J.:* Acta radiol. 1944, *25:* 845—855.
19) *Videbæk, Aa.:* Heredity in Human Leukemia and Its Relation to Cancer. Lewis & Co. Ltd. London, 1947.
20) *Videbæk, Aa. & J. Mosbech:* Acta med. scand. 1954, *149:* 137.
21) *Walton, J.:* Lancet 1936, *I:* 1101—1107.

BRONCHIAL CARCINOMA — A PANDEMIC

II.

INCIDENCE AND TOBACCO CONSUMPTION IN VARIOUS COUNTRIES

By ARNE NIELSEN and JOHANNES CLEMMENSEN

The increase in incidence of bronchial carcinoma observed in various countries has, so far, largely been limited to the male sex (16), even if there are recent reports of a beginning increase among women, particularly in U. S. A. Among men the increase has particularly affected the younger part of the middle-aged groups, but is gradually extending to older age groups as the birth groups — or cohorts — affected are coming of age (16). Since the increase is more advanced in urban than in rural areas and more among the poor than among the wealthy (2), there will be a natural tendency to limit comparisons between countries to data on men living in towns, preferably under identical social conditions.

During the last years a number of authors previously reviewed (Doll & Hill, Wynder & Graham, Levin et al., Sadowsky, Gilliam & Cornfield etc.) have reported on inquiries among patients suffering from bronchial carcinoma and among control persons and have established that smokers of tobacco, particularly cigarettes, are more subject to the risk of bronchial carcinoma than non-smokers. It would now seem desirable also to examine the interrelation of tobacco consumption and the risk of bronchial

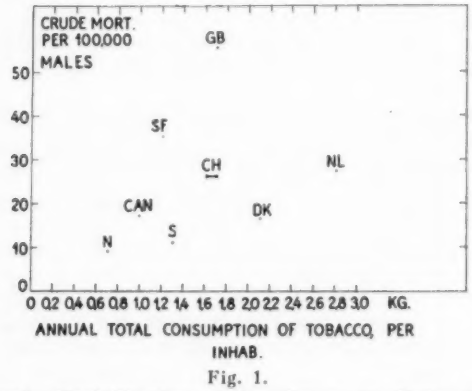


Fig. 1.

Crude Mortality from Lung Cancer in Males for various Countries about 1950 plotted against annual total consumption in kg. of tobacco per inhabitant about 1930.

N signifies Norway, S Sweden, CAN Canada, DK Denmark, CH Switzerland, NL The Netherlands, SF Finland, GB England-Wales.

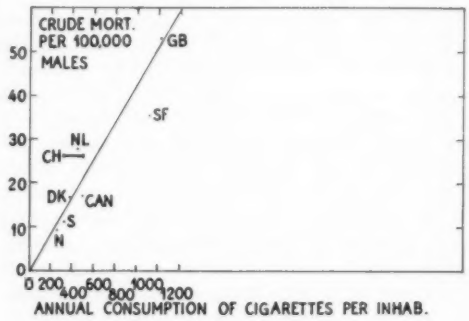


Fig. 2.

Crude Mortality from Lung Cancer in Males for various Countries about 1950 plotted against annual total consumption of cigarettes per inhabitant about 1930.

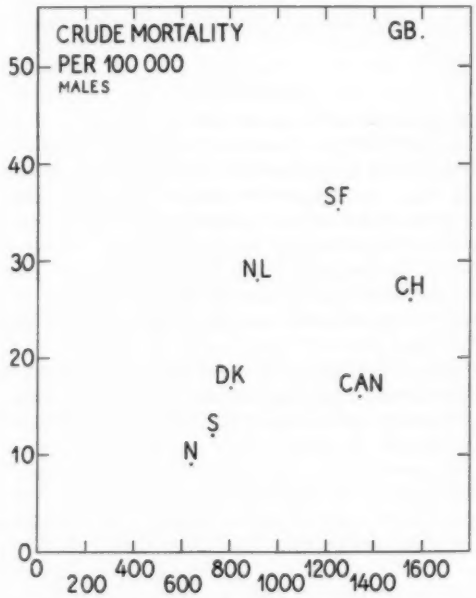


Fig. 3.

Mortality from Lung Cancer as in figg. 1 and 2 plotted against contemporary consumpttion of cigarettes about 1950.

From the Danish Cancer Registry under the National Anti-Cancer League.

Part of a paper read at The International Congress of Geographical Pathology, Washington, D. C., Sept. 10, 1954.

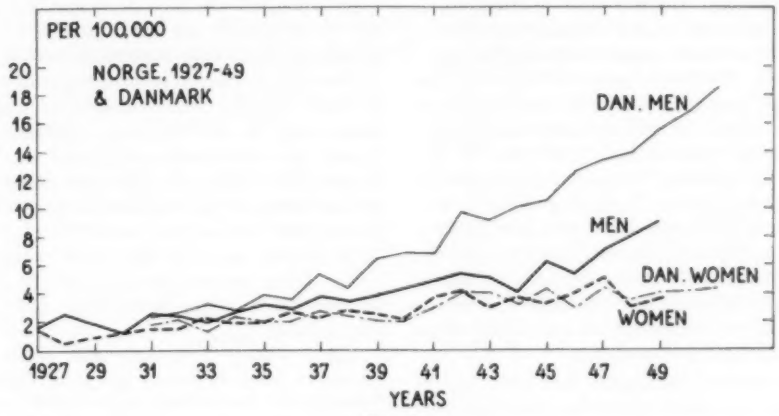


Fig. 4.
Norway, 1927—49. Crude Mortality Rates for Cancer in the Respiratory System. (14, 18).

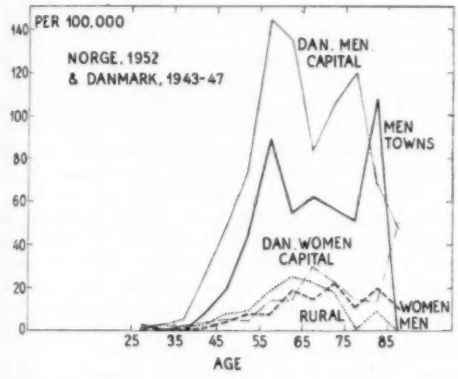


Fig. 5.
Norway, 1952. Morbidity Rates at various Ages for Cancer in Lung and Bronchus (162, 163). By courtesy Dr. Einar Pedersen, Cancer Registry of Norway. (Denmark (4)).

carcinoma on a demographical basis. However, since figures for tobacco consumption will apply to whole countries such studies must be based on the total number of bronchial carcinomas in each country, even if such methods cannot claim the accuracy of studies limited to smaller areas.

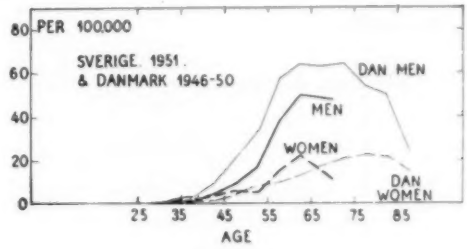


Fig. 6.
Sweden, 1951. Mortality Rates at various Ages for Cancer in Lung, Pleura, Trachea and Bronchus. From N. Ringertz.

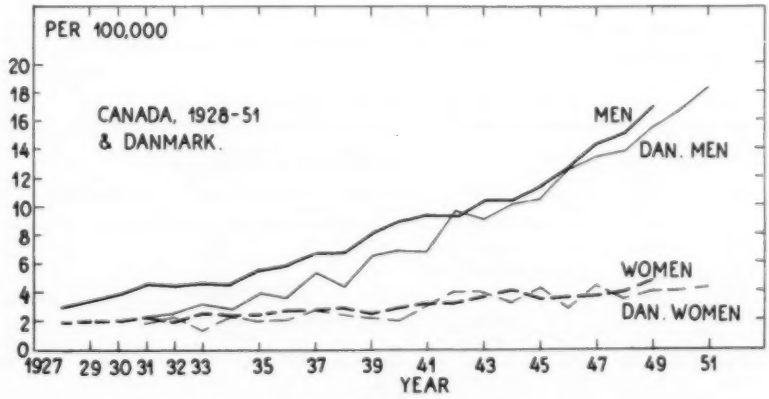


Fig. 7.
Canada, 1928—51. Crude Mortality Rates for Cancer in the Respiratory System. (14, 18).

The International Society for Geographical Pathology for its congress in Washington, D. C., in September 1954 made inquiry among its members in various countries with a view to the incidence of bronchial carcinoma. It is true that the material collected would in most cases apply to mortality from this disease, but due to the shortcomings of therapy these figures will on the whole be adequate as incidence figures. For our report on this inquiry the present authors collected supplementary information in order to examine the interrelation between national figures for tobacco consumption and incidence of bronchial carcinoma in a number of countries to be briefly reported in the following.

It is in the matter of things that figures like these will only be approximately correct. Quite apart from the influence of smuggling and other sources of error it will never be possible to estimate accurately the relative tobacco consumption for the two sexes in the various countries about two decades ago, and for this reason we have in the following given the total consumption while figures for mortality of cancer of the lung are given for the male sex under the assumption that for the periods in question the values of both categories will in the main be determined by the values for males.

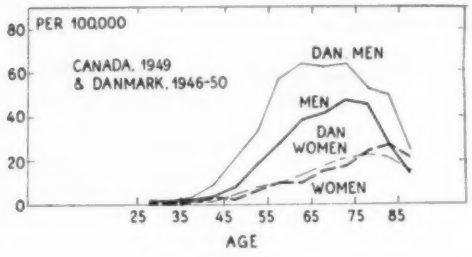


Fig. 8.

Canada, 1949. Mortality Rates at various Ages for Cancer of Lung (162, 163). From Canad. Bur. Stat.

In previous studies reviewed in this journal (p. 44 ff. 1954) we have found it justified to postulate an average minimum period of exposure to the factors causative of bronchial carcinoma of at least twenty years as far as Copenhagen is concerned (5, 4). We have, therefore, in figures 1 and 2 — previously published in *Ugeskrift for Læger, 116:* 1294—95, 1954 — plotted the national consumption of tobacco for a number of countries about 1930 against the mortality of cancer of the lung among men in the same countries twenty years later, which method to the best of our knowledge has not previously been applied on this subject.

Fig 1 shows that although some correlation seems to exist between the total consumption of tobacco per individual in the countries concerned about 1930 and the crude mortality figures for cancer of the lung in 1950, it is less striking than might be expected. Hovewer, when as in figure 2 the annual consumption of *cigarettes* about 1930 is plotted against crude mortality figures for cancer of the lung about twenty years later it is clear that countries with a high consumption of cigarettes are almost certain to show a correspondingly high mortality from cancer of the lung among males two decades later.

It may be asked what would have been the result had the consumption to-day of cigarettes in the various countries been plotted against the contemporary mortality figures for cancer of the lung. This possibility is illustrated in fig. 3.

It appears that in this case a line through the average values will not pass through O. Hovewer, it will not be possible to make a detailed comparison between fig. 3 and fig. 2, because the proportion of women smoking cigarettes will have changed to an unknown extent, probably differing between the countries.

Since figures 1—3 have been based on crude mortality rates the authors felt the desirability of a more detailed documentation of the differences in mortality from cancer of the lung in the countries studied, with the exception of

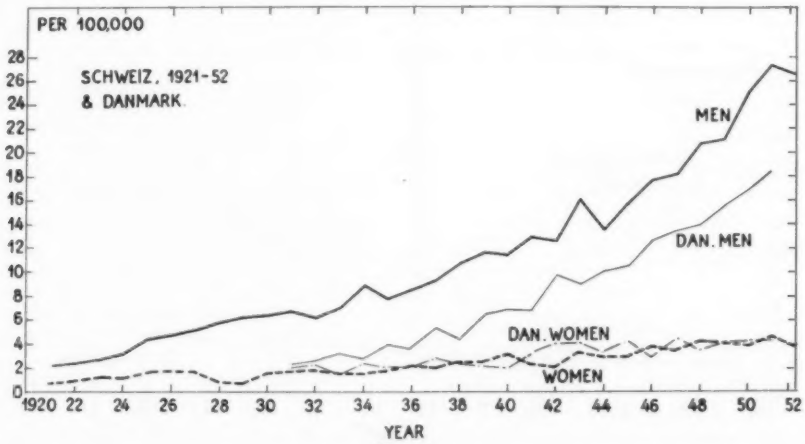
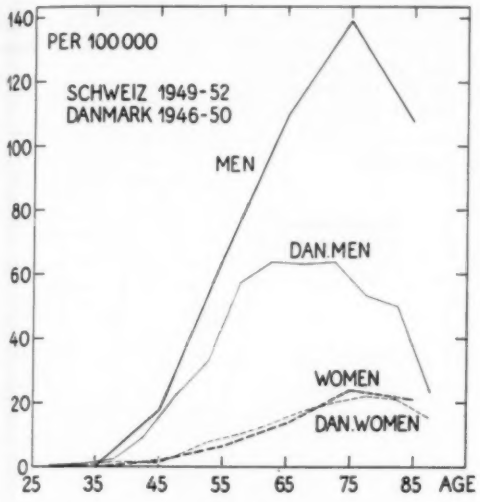


Fig. 9.

Switzerland, 1921—52. Crude Mortality for Cancer of Lung and Bronchus. (1, 15). From O. G s e l l.

Norway for which incidence figures are available. We have, therefore, added the following diagrams worked out on the basis of information provided by workers in various countries for the congress of Geographical Pathology. The figures for each country have been compared with corresponding Danish figures as a common denominator.



Fif. 10.
Switzerland, 1949—52. Mortality Rates at various Ages for Cancer of Lung and Bronchus. From O. Gsell.

For Switzerland and The Netherlands it has further been possible to work out the mortality from cancer of the lung for groups born in the same year, i. e. cohorts, and the results are shown in the figures 17, 18 and 19 given below. Corresponding diagrams for England and Denmark have previously been published in this journal (pp. 41 and 44) and it seems that there is considerable similarity in the results of this analysis of which the principle was originally laid down by R. Korteweg.

ACKNOWLEDGEMENT

The authors are obliged for information on figures for the mortality and incidence from cancer of the lung as well as on tobacco consumption from the following scientists:

Professor O. Gsell, Basel, Miss A. Korpela, Helsinki, Dr. R. Korteweg, Amsterdam, Director, Dr. Einar Pedersen, Oslo, Professor N. Ringertz, Stockholm, Dr. E. Saxen, Helsinki, Dr. Percy Stocks, London, and to the Canadian Bureau of Statistics and Eidgenössisches Statistisches Amt, Bern.

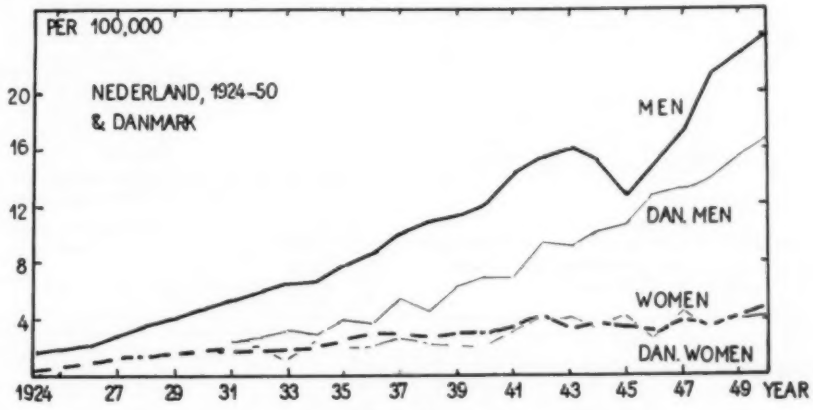


Fig. 11.
The Netherlands, 1924—50. Crude Mortality Rates for Cancer of the Lung. (8).

Table 1.
Countries in Order of Magnitude of Crude Mortality of the Lung in Males.

	Cancer of the Lung Crude Mortality pr. 100,000			Annual Consumption per Inhabitant					
	Year	Males	Females	Year	Total Tobacco kg	Cigarettes no.	Year	Total Tobacco kg	Cigarettes no.
Norge	1952	9.2	4.4	1930	0.7	257	1951	1.2	641
Sverige	1951	11.1	4.3	1930	1.3	320	1951	1.4	624
Canada	1949	17.0	4.8	1930	1.6	491	1950	2.5	1339
Danmark	1951	18.4	4.3	1930	2.1	373	1951	2.2	809
Schweiz	1952	26.4	3.7	1926 1934-37	1.6 1.7	302 489	1952	2.5	1545
Nederland	1952	28.3	3.3	1931	2.8	444	1952	2.3	913
Finland	1950	35.3	6.1	1930	1.2	1106	1950	1.4	1146
England-Wales	1951	53.0	9.1	1930	1.7	1200	1951	2.0	1600

REFERENCES

1) Bevölkerungsbewegung in der Schweiz.
2) *Clemmesen, J. & Arne Nielsen:* Brit. J. Cancer, 1951, *V:* 159.
3) *Clemmesen, J. & Arne Nielsen:* Ugeskr. f. Læg. 1954, *116:* 1294.
4) *Clemmesen, J., Arne Nielsen & Emmerik Jensen:* Acta Internat. Cancer, 1953, *9:* 603 (16).
5) *Clemmesen, J., Arne Nielsen & Emmerik Jensen:* Brit. J. Cancer, 1953, *VII:* 1.
6) *Clemmesen, J.:* This journal, 1954, 37.
7) *Kennaway, E. L. & N. M. Kennaway:* Brit. J. Cancer, 1947, *I:* 260.
8) *Korteweg, R.:* Acta Internat. Cancer, 1953, *9:* 589 (16).
9) *Kreyberg, H. J. A.:* Brit. J. Cancer, 1954, *VII:* 13.
10) *Phillips, A. J.:* Mortality from Cancer of the Lung in Canada 1931—1952. Canad. Med. Assoc. J., 1954, *71:* 242.
11) Registrar Gen. Statist. Rev. Part 1, Medical.
12) Registrar Gen. Statist. Rev. Part 2, Civil.
13) Statistical Yearbook of Canada.
14) Statistical Yearbook of Denmark.
15) Statistiches Jahrbuch der Schweiz.
16) Symposium on Endemiology of Cancer of the Lung. Editor: C. I. O. M. S., Paris 1953.
17) W. H. O. Annual Epidemiological and Vital Statistics 1947—49 and 1950. Part 1: Vital Statistics and Causes of Death.
18) W. H. O. Epidemiological and Vital Statistics. Report V, nos. 1—2, 1952.

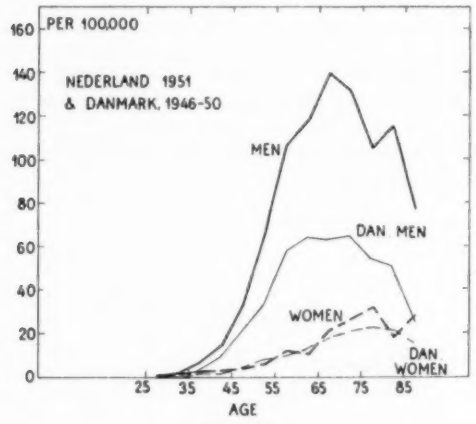


Fig. 12.
The Netherlands, 1951. Mortality Rates at various Ages for Cancer of Lung and Bronchus (162, 163). From C. A. G. Nass.

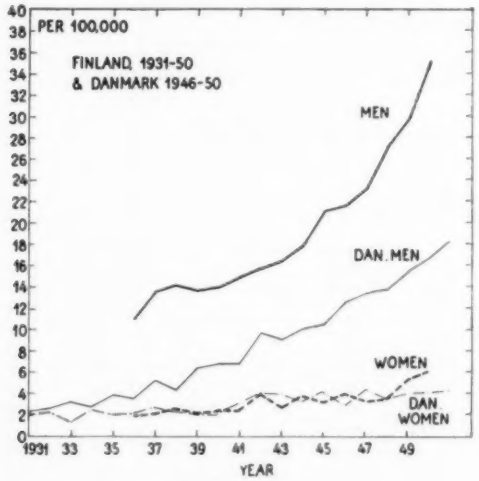


Fig. 13.
Finland, 1931—50. Crude Mortality Rates for Cancer of Lung and Larynx. (14, 18).

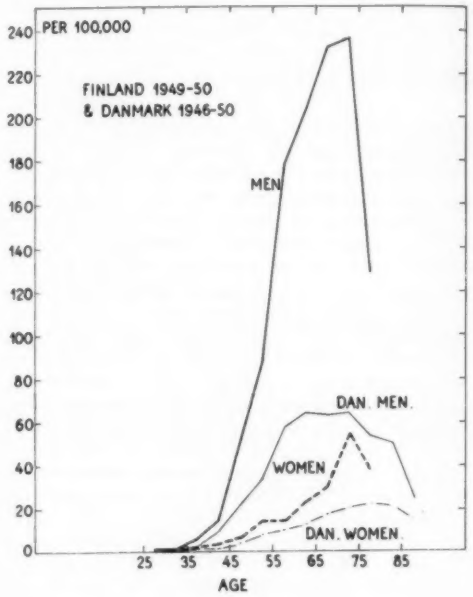


Fig. 14.
Finland, 1949—50. Mortality Rates at various Ages for Cancer of Lung and Larynx.

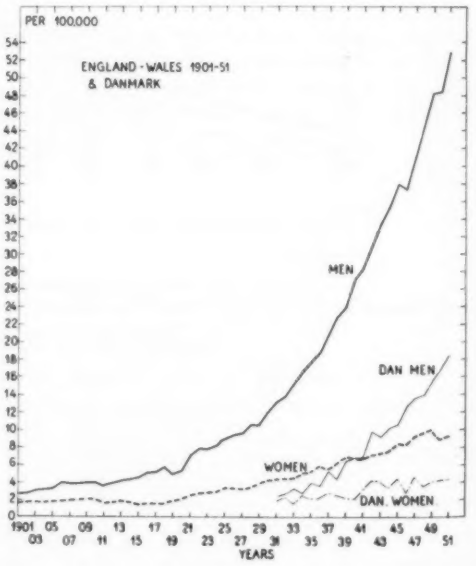


Fig. 15.
England-Wales, 1901—51. Crude Mortality Rates for Cancer of Respiratory System. (12, 18).

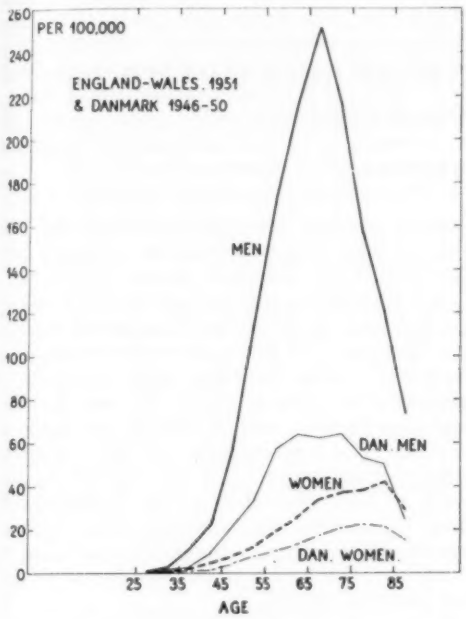


Fig. 16.
England-Wales, 1951. Mortality Rates at various Ages for Cancer of Lung and Bronchus (162, 163). From P. Stocks. (11).

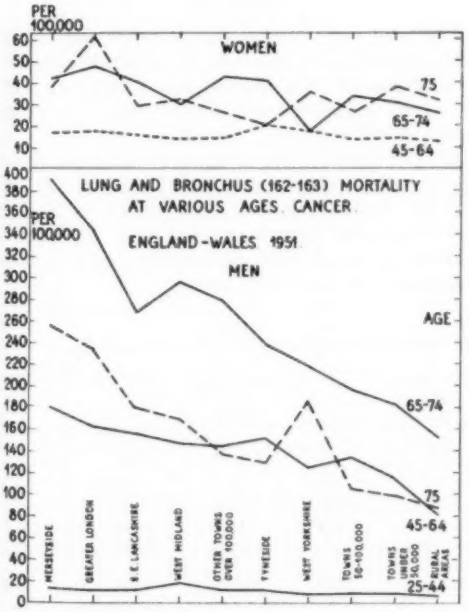


Fig. 17.
Various Regions England-Wales, 1951. Mortality Rates at various Ages for Cancer of Lung and Bronchus (162, 163). P. Stocks. (11).

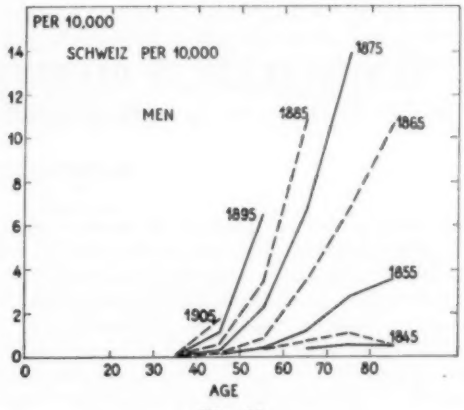


Fig. 18.
Switzerland. Mortality from Cancer of Lung and Bronchus for Cohorts born about Year indicated. From O. Gsell. (1).

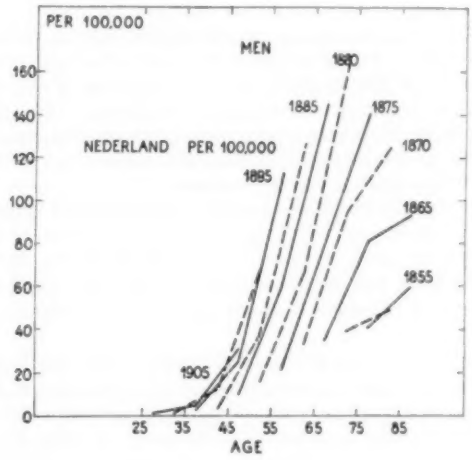


Fig. 19.
The Netherlands. Mortality from Cancer of the Lung and Bronchus for Cohorts born about Year indicated. From R. Korteweg.

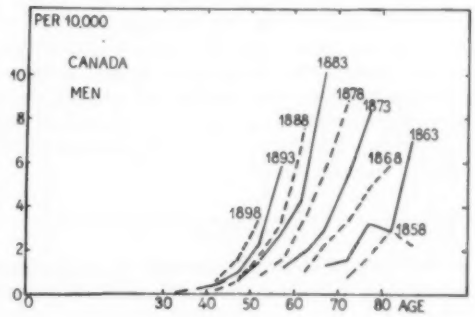


Fig. 20.
Canada. Mortality from Cancer of Lung for Cohorts at various Ages. (10).

ALBUMINURIA IN DIABETES AND ITS RELATION TO AGE AT ONSET OF DIABETES

By KARL ANKER STEFFENSEN

The most prominent question in recent research on late diabetic complications is the value of very accurate control and treatment in its present form in preventing or postponing complications. To solve the problem definitely, attention must be paid to other characteristics of the patients and their disease than those concerning treatment and control. Comparison of the frequency of complications in series of patients treated in different ways or under different degrees of control may be difficult if differences in other respects cannot be excluded. It would also be useful if new principles could be added to the present insufficient treatment, by investigation of other factors.

The diabetic renal complications which form the theme of this study, may have a varying clinical and histological picture including a more or less pronounced nephrotic syndrome. One of the most consistent single signs of these complications is albuminuria, usually intermittent at first and constant in the later stages.

It is known that diabetic nephropathy may arise in patients of all ages and that the frequency increases with the duration of the diabetes. But only little has been published about the significance of the age at which the diabetes commenced.

Bjerkelund found no difference in frequency of nephropathy whether the diabetes commenced before or after 40 years of age. However, rapid development of renal disease, i. e. after less than 5 years of diabetes, was more frequently found in patients whose diabetes had been diagnosed after the age of forty.

Keiding, Marble and Root found a smaller number of complications in the best controlled groups in patients whose diabetes had started before the age of 30 and further made a remarkable observation concerning the nephropathies. These complications were found earlier and more frequently in patients whose diabetes had begun between the ages of 10 and 19 years than in those from the groups of 0—9 and 20—29 years and this difference was independent of the quality of the treatment.

MATERIAL

In the present study the records of all patients with diabetes admitted to the 3 medical departments of Gentofte Amtssygehus during the years 1945—52 were reviewed. Patients admitted more than once were classified mainly according to the last hospital record. The age at which the disease had been diagnosed was established from the case histories, and the cases with "constant albuminuria" sifted out. The term "constant albuminuria" is taken to mean: All tests for albumen were positive, and at least 3 had been carried out. The total number of tests depended largely on the duration of the stay in hospital which in turn depended on the conditions for which the patients were admitted. Cases with one negative albumen test — but never more than one — were included only if the number of positive tests was at least five.

The material obtained in this way comprises practically all patients with fully developed nephropathy while some of those in incipient stages are excluded. A small group of cases in which the diabetes and the renal disease are independent of each other is however included, but with our present knowledge, this group is very difficult to define.

RESULTS

The total material consists of 1187 patients. In 1138 (96 per cent.) the time at which the diabetes was diagnosed was stated. 443 were men (38,9 per cent.) and 695 were women (61,1 per cent.). Constant albuminuria was found in 150 cases (13,2 per cent.). The frequency of albuminuria was nearly equal in men and women, 13,8 and 12,8 per cent. respectively. As shown in Table 1, this frequency increases with the duration of diabetes to 25 per cent. in patients whose diabetes had lasted 15 years and more:

Table 1.

Duration of diabetes years	No.	Percentage of all cases	Constant albuminuria	
			Numbers	Percentage
0—2	382	33.6	26	6.8
3—7	219	19.3	18	8.2
8—14	281	24.7	41	14.6
15—24	213	18.7	54	25.4
25 and over	43	3.8	11	25.6
Total	1138	100.0	150	(13.2)

The duration of diabetes when the renal lesion was found varied as shown in Fig. 1. The cases are collected in 3 years groups. The most remarkable feature is the presence of 2 peaks, one be-

From Gentofte Amtssygehus, Medical Departments B, C and F. Senior physicians: *E. Rosling, M. Siggaard Andersen* and *F. Wulff.*

tween 12 and 20 years duration and one in the group 0—2 years. This, apparently, indicates that at least 2 types of albuminuria are represented. However, it must be emphasized that the first column of the figure probably is artificial. It consists of 26 cases, 18 of which had constant albuminuria at the time when the diabetes was diagnosed. All of them were older patients and probably many of them had albuminuria for some time before the diabetes was found.

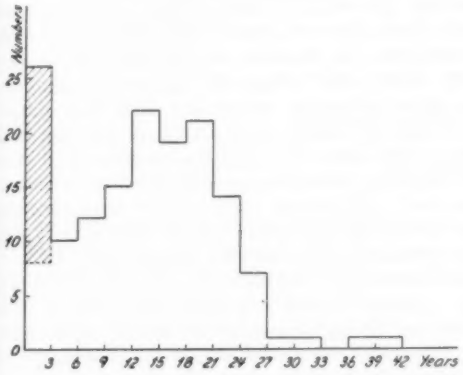


Fig. 1.
Cases of albuminuria arranged in groups according to the length of interval between the diagnosing of diabetes and the demonstration of constant albuminuria. Hatched area: diabetes and albuminuria found simultaneously.

Fig. 2 shows the correlation between the duration of diabetes and the age at the commencement of diabetes in the 150 cases. The points are grouped in a way indicating that the "time for development" of nephropathy is shortest when diabetes commenced about the age of 10—15

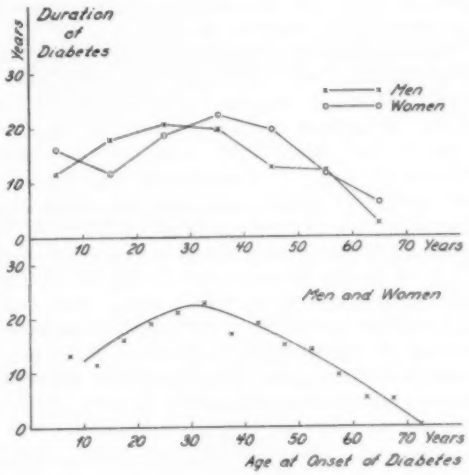


Fig. 3.
Relation between the duration of diabetes when constant albuminuria was found and the age at which the diabetes was diagnosed. Above: average values for 10-years groups, below: average values for 5-years groups.

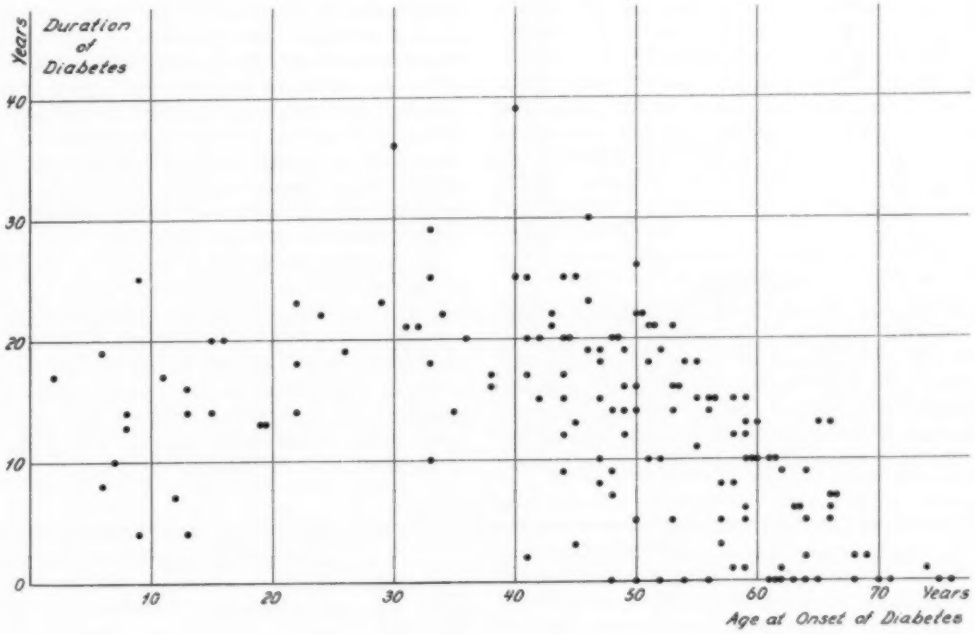


Fig. 2.
Relations in all cases between the duration of diabetes when constant albuminuria was found and the age at which diabetes was diagnosed.

years and increases gradually to maximum for patients whose diabetes starts at the age of 30—35, and then decreases during the following decades.

In Fig. 3 the curves are drawn by means of average values for 5- and 10-years groups from Fig. 2. The curves for men and women assume the same form, but the curve for men reaches its maximum before that for women.

The incidence of albuminuria among patients whose diabetes was diagnosed at varying ages is shown in Table 2. As about one third of the total number of patients had had diabetes for less than 3 years (and apart from some of the elderly patients no case of albuminuria was found in this group) it might influence the result in a misleading way if these cases were included. The comparison therefore is made in two ways, being based on 1) the whole material and 2) all cases with diabetes lasting at least 3 years. Both tables show minor variations for diabetes which commenced at the ages 0—39. Maximal incidence is found in the age group 40—49, but the difference has no statistical significance.

Table 2.

Age at onset of diabetes	Total material		Diabetes 3 years and over	
	Numbers	Albuminuria per. cent.	Numbers	Albuminuria per. cent.
0—9 ..	58	13.8	50	16.0
10—19 ..	109	9.2	82	12.2
20—29 ..	89	6.7	68	8.8
30—39 ..	109	11.0	76	15.8
40—49 ..	180	21.1	144	25.0
50—59 ..	293	14.7	209	17.7
60—69 ..	209	12.4	108	13.9
70—89 ..	91	7.7	19	0.0
Total ...	1138	13.2	756	16.4
Men 0—39			123	15.4
» 40—49			47	31.9
Women 0—39.....			153	11.1
» 40—49.....			97	22.7

DISCUSSION

The form of the curves in Fig. 3 indicates that the interval from the commencement of diabetes until full development of nephropathy depends, in some way, upon the age at which the diabetes commenced, increasing during the first decades to the age of 30—35. Later in life, the interval for development of nephropathy seems to be shorter the older the patient is at the commencement of diabetes. The course of this part of the curve approaches a line which indicates the manifestation of renal disease as a function of the aging of the patient and independent of the age at which the diabetes was diagnosed.

The cases in which diabetes and albuminuria was found simultaneously are indicated in Fig. 2 by points on the abscissal axis. Probably some of them should be placed below the line, were the pre-existance of albuminuria before the diabetes known. The way in which these points fall suggests that they are within the limits of natural dispersion. As diabetes in old persons often is very mild and diagnosed by mere chance, it is often uncertain when the diabetes actually commenced. But, if it is accepted that the majority of the cases of constant albuminuria in elderly diabetics have some causal relation to diabetes the best explanation must be that both disorders are result of the same causal factors and only accelerate one another to a minor degree.

In the first 4 decades, it seems inevitable that the diabetes should be present for some years before the development of constant albuminuria, and other factors than those dominating in old age seem to be present. According to the investigations of K e i d i n g, M a r b l e & R o o t and to the results of this study, those factors must be supposed to be most potent about the age of puberty and to decrease during the subsequent years.

If different causal factors are active in various periods of life, we must also expect different clinical pictures. The patients in this material representing 3 medical departments and a period of 8 years were not examined in such a uniform manner that a thorough analysis of the character of the renal disease can be made. However, some details of 3 groups of patients are shown in Table 3. Each group consists of 12 patients and includes all cases in which the diabetes was diagnosed in certain age intervals.

The gravity of the renal disease is illustrated by the last columns of the table. Impaired renal function was found in all groups, particularly the intermediate group in which the highest blood pressure values were also found. Severe proteinuria and high blood pressure was less pronounced among the patients whose diabetes had started in youth than in the other groups. The frequency of pyuria seems to increase with age.

Table 3.

Age at onset of diabetes	Insulin daily i. u.	Albuminuria ‰	Albuminuria ≥ 2 ‰ Numbers	Albuminuria gm/day	gm/day Average	Pyuria Numbers	Blood pressure (Average for 12 patients) Highest syst.	Highest diast.	Lowest syst.	Lowest diast.	Impaired renal function Numbers
5—14	70	0.3— 4.5	1	0.3—6.3	2.0	4	155	100	129	79	4
30—39	38	0.5—12.0	5	0.5—8.4	3.7	6	207	115	161	81	6
50—52	18	0.2—10.5	5	0.1—8.4	3.1	8	179	104	152	78	3

Summary.

The records of 1187 diabetic patients admitted to 3 medical departments during an 8 year period were reviewed. The incidence of constant albuminuria was found to be 13,2 per cent., nearly equal in men and women. Renal complications were most frequently found in patients whose diabetes started between 40 and 50 years of age but the variations were too small to permit definite conclusions. The duration of diabetes until the finding of constant albuminuria varied in a remarkable way with the age at which diabetes commenced, being shortest for the period of puberty and in old age and longest for diabetes started in the age of 30—35. It is suggested that different causal factors are present at different ages.

References:

1) *Bjerkelund, C. J.:* Acta med. Scand. 1951, *139:* 133.
2) *Keiding, N. R., H. F. Root & A. Marble:* J. A. M. A. 1952, *150:* 964.

SALT-LOSING NEPHRITIS

By STEFFEN GJØRUP

Under the name of salt-losing nephritis Thorn, Clinton & Koepf (11) in 1944 described the clinical picture of a chronic renal disease with an extraordinary great urinary loss of sodium.

Although acute glomerulonephritis and nephrosis are generally accompanied by retention of sodium, a loss of this ion is not infrequently seen in patients with chronic glomerulonephritis and pyelonephritis. Usually this loss is only moderate and does not require special precautions other than a diet rich in sodium chloride.

On the contrary the output of sodium in the urine in patients with salt-losing nephritis is so large, that the sodium depletion dominates the clinical picture. Several of the cases reported in the literature have been diagnosed and treated as patients with acute adrenal insufficiency until the true nature of their disease was revealed.

In their original paper (11) Thorn and his associates present the history of two young men without any previously known renal disease. They were admitted in shock-like conditions with hypotension and haemoconcentration. The low values for serum sodium and a negative routine urinalysis lead to the diagnosis of acute adrenal insufficiency. The patients responded well to adequate treatment with intravenous sodium chloride and desoxycorticosterone. After restoration of plasma volume and blood pressure, however, azotaemia persisted. Further balance studies failed to show any effect of adrenal hormones on the sodium balance. The authors therefore concluded that the disease must have been of renal origin, and the chief symptoms due to failure of the tubules to conserve sodium in a normal way.

This report was followed by a paper by Borst (1), who in 1949 published a detailed investigation of a patient with polycystic kidneys. The patient suddenly developed a severe subacute renal insufficiency requiring a daily administration of more than 100 gms. of sodium chloride. Joiner & Thorne (5) reported 3 cases of salt-losing nephritis with symptoms closely resembling those of Thorn's patients. They added a new symptom, since 2 of their 3 patients showed pathological pigmentation, in one case involving the classical Addisonian areas on the buccal mucosa and the pressure points. This finding leads to further difficulties in making the important differential diagnosis from Addison's disease. Similar cases have been presented by other authors (2, 3, 7, 8, 9), and at present 13 cases have been reported in the literature. Murphey (6) emphasizes the importance of early recognition of the sodium loss in patients with chronic renal insufficiency and impending uraemia since proper treatment with sodium chloride may lead to gratifying therapeutic results. He stresses that the disease need not start with the alarming Addisonian picture outlined above as this seems to be the »crisis« in the disease. He suggests the that name be changed to »salt-losing syndrome«.

The pathological changes in the kidneys were discussed by Enticknap (4) in 1952. He summarizes the pathological and histological details of the cases published already and adds personal observations and studies of 3 cases. He concludes that chronic pyelonephritis was certainly present in 4 cases, probably in 2 and might have been present in all 8 cases. Histologically he never found any signs of acute glomerulonephritis but always extensive tubular changes similar to those found in chronic pyelonephritis. He suggest the name »chronic interstitial nephritis« since the presence of chronic inflammatory exudate and interstitial fibrosis are main features in combination with the tubular degeneration. He is unable to demonstrate any specific genesis of the lesions as they seem to originate from congenital anomalies (cystic kidneys) and also from pyelonephritis and renal tuberculosis.

From Medical Department A, Rigshospitalet, Copenhagen. Chief: Professor *K. Brøchner-Mortensen.*

Case report: Our patient is a 36 year-old clerk. At the age of 9 years he developed knock-knees and underwent orthopaedic surgery on both femurs at the age of 11. One year later, the defect reappeared. For this reason and because of retardation of growth, at the age of 14 years, he was admitted to the childrens' department of the Copenhagen University Hospital (J. No. 365/1932). Here a diagnosis of renal rickets was made (10). Physical and laboratory examinations did not reveal any bone disease with the exception of the deformity of the knees. The values of serum calcium and phosphorus were normal. The urinary output of calcium was low and that of phosphorus was normal. The urinalysis disclosed a low specific gravity (1005—1008), a rather large diuresis (2—3 litres), maximum concentration power up to 1009, daily minimal quantities of albumin (max. ¼ ‰ Esbach), occasionally some white cells, less frequently red cells and never casts. The blood pressure was normal 115/55. The blood urea varied between 53—68 and 17 mg per 100 ml. X-ray examination showed small calcifications around the renal pelves and calyces on both sides. During the stay in the department the clinical condition improved, and as he appeared to grow normally, he was discharged.

During the next 20 years the patient felt absolutely well. In Nov. 1952 he suddenly developed anorexia, general malaise and severe cramps in both legs. The symptoms were progressive and 8 days after the onset of the illness he was admitted to Medical Department A of Copenhagen University Hospital for the first time. On admission he was dehydrated, uraemic and acidotic. Examinations of the blood disclosed the following values: blood urea 352 mg per cent., bicarbonate 9 mmol, chloride in serum 78 mmol and calcium in serum 10 mg per cent. Considerable improvement occurred following treatment with sodium bicarbonate and -chloride solutions in the course of 10 days. On discharge, the blood urea had fallen to 61 mg per cent. and the values of serum bicarbonate and chloride were normal. X-ray examination revealed normal density of the bones and numerous small calcifications in both kidneys.

During the 14 months following discharge he appeared to be well until, in Feb. 1954, he caught a severe cold. Following this he complained of weakness, headache and painful legs but not of nausea nor vomiting. He consulted the out-patient clinic of the hospital and blood examinations there showed uraemia, acidosis and chloropenia. Analysis of the urine showed albuminuria, but no cells or casts were seen on microscopy. 3 days later after a heavy nose bleeding the symptoms became aggravated, and he was again admitted to the Department A. On admission, he was dehydrated and the skin was covered with »urea-frost«. The laboratory findings were as follows: Blood urea 391 mg per cent., bicarbonate in serum 16 mmol, chloride in serum 77 mmol, sodium in serum 114 meq per litre and potassium in serum 4·25 meq per litre. X-ray of the chest showed a blurred shadow in the lower part of the left lung. Since the rectal temperature was rather high these changes were considered to be due to pneumonia. Administration af antibiotics was started together with intravenous treatment of the renal insufficiency with electrolytes and water. During this regime he improved gradually despite copious diuresis (3—6 litres per 24 hours, specific gravity 1004—1007). No cells nor casts were found in the urine, but a trace of albumin occurred regularly (max. 0.7 ‰ Esbach). The blood pressure was normal. Values of serum calcium 10—9 mg per cent. and of serum phosphorus 4,3—5,2 mg per cent. In spite of the extensive replacement therapy with sodium chloride the sodium and chloride in the blood remained low. The 24-hours excretion of sodium in the urine was therefore measured and found to be extremely high, averaging 470 meq Na+ which is equivalent to about 30 gms of NaCl. Accordingly we continued to give the patient a salt-rich diet (about 10—15 gms. daily) + an extra supply of 15—20 gms. of sodium chloride per day. Following this regime the patient became more alert and felt stronger. The daily laboratory findings are shown in figure 1.

The diagnosis in this case was not difficult. The previous renal history, the excessive output of sodium in the urine and the electrolyte pattern during the treatment made the diagnosis of salt-losing nephritis most probable.

The treatment consisted of replacement of the urinary loss of sodium and water. The first days the sodium containing solutions were given parenterally. During this treatment the patient suddenly became unconscious. Examinations showed a very low serum potassium value. Probably he had developed a hypopotassaemia (sodium-potassium exchange in the cells?) during the extensive sodium replacement. Treatment with potassium promptly improved the condition. The patient very soon tolerated a salt-rich diet, and the extra supply of 15—20 gms. of NaCl and 5 gms. of sodium bicarbonate was administered as enteric coated tablets. With this prescription he was discharged from the hospital.

DISCUSSION

The previously recorded cases together with the observations in this case of renal insufficiency with extremely negative sodium balance support the conception of a special type of chronic renal disease called salt-losing nephritis.

The etiology and the pathological findings possibly suggest that salt-losing nephritis is only a symptom of chronic renal disease, occuring in those cases with the most extensive tubular damage. The striking clinical picture and the gratifying therapeutic results, however, seems to justify

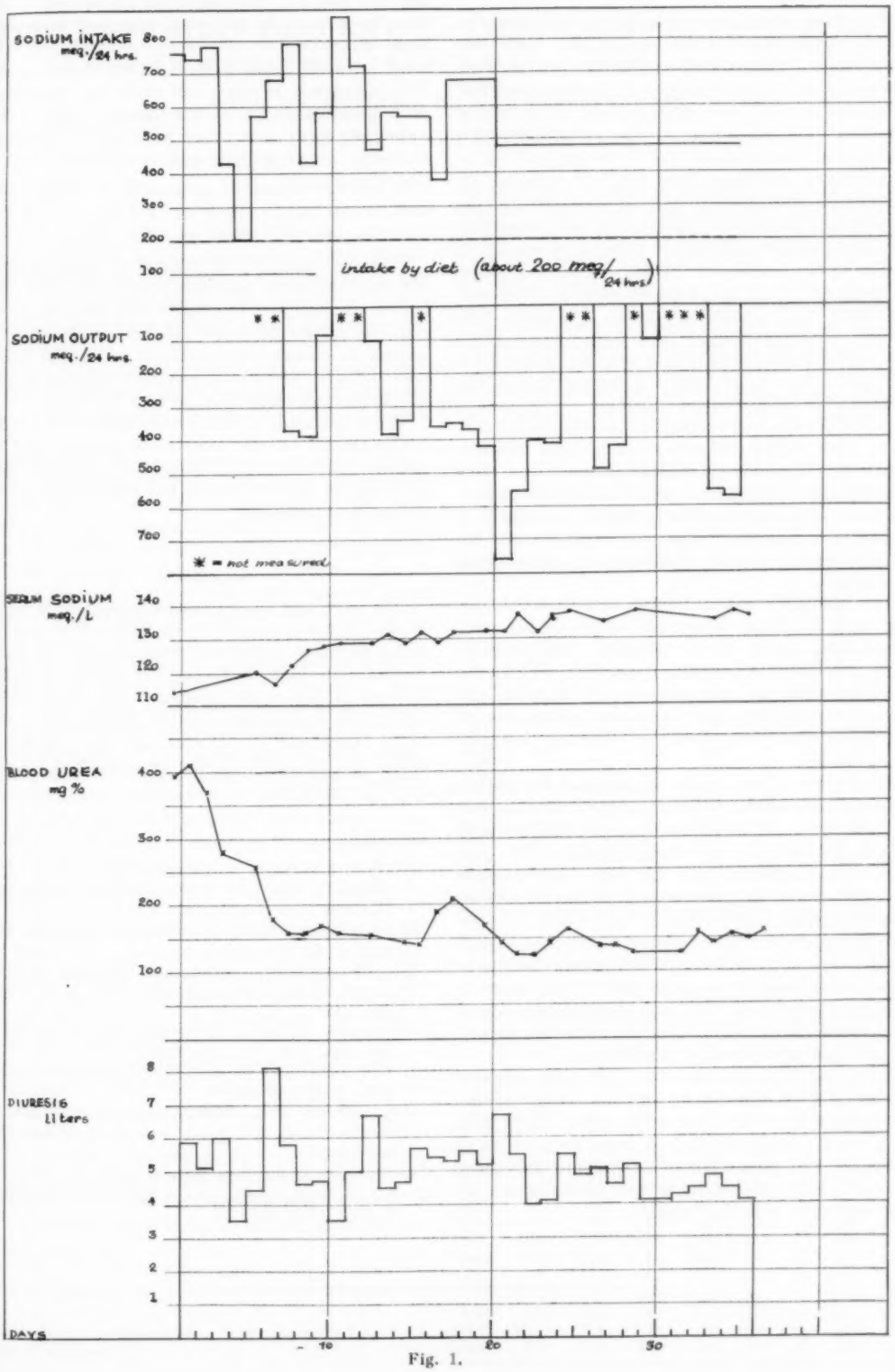

SODIUM INTAKE
meq./24 hrs.
800
700
600
500
400
300
200
100
intake by diet (about 200 meq./24 hrs.)
SODIUM OUTPUT
meq./24 hrs.
100
200
300
400
500
600
700
* = not measured
SERUM SODIUM
meq./l
140
130
120
110
BLOOD UREA
mg %
400
300
200
100
DIURESIS
Liters
8
7
6
5
4
3
2
1
DAYS
10
20
30

Fig. 1.

the description of this condition as a well defined clinical syndrome.

Clinically, salt-losing nephritis is a progressive nephropathia. The symptoms arising from the deprivation of essential substances as sodium chloride from the body are main features and the failure to excrete nitrogenous and other waste products recedes. Some of the recorded cases imply that the disease has been present in a latent form for some time until it appears in connection with intercurrent diseases (frequently infectious). The latent renal defect then manifests itself through the inability to retain sodium. Prior to the acute onset, the patient have very often complained of general malaise, apathy, muscular weakness and cramps, anorexia, headache and nausea. These symptoms are well known from the mild salt-depletion which may be induced by salt restriction prescribed together with the administration of mercurial diuretics.

It seems very characteristic that adequate treatment with rapid restoration of sodium balance strikingly improves the clinical condition. Obviously, the underlying renal disease determines the inevitable prognosis of death in uraemia, but the early recognition of the salt-depletion and its proper treatment may postpone the impending uraemia.

The published cases of salt-losing nephritis are few and investigations on the nature of the condition are scanty. It is, therefore, not possible with certainty to establish whether all of the recorded clinical and pathological findings are specific to the disease, concurrent symptoms of the same basic condition, or, perhaps, entirely unconnected.

Sawyer & Solez (9) suggest that the pathological pigmentation, which may resemble the Addisonian type, is due to dysfunction of the adrenal glands provoked by the abnormal electrolyte pattern. They support this by the hypertrophic adrenals found at the autopsy of their patient. Following this observation Joiner & Thorne (5) demonstrated the presence of adrenal hypertrophy in 2 of their 3 cases. Reviewing the literature concerning the 9 cases which have come to autopsy to date, adrenal hypertrophy was found in 5 cases (5, 6, 9, 11). This supports the theory of concomitant adrenal dysfunction.

Some authors describe changes in the calcium metabolism. Calcifications of the renal parenchyma are found in 4 out of 10 cases (5, 9, 11 & own case) and parathyroid hypertrophia in 3 cases (5, 11). It is difficult to exclude that these parenchymal calcifications are contributory to the extensive tubular damages.

In 1954 Cheyne & Whitehead (2) stress the fact that 3 of the cases put on record at that time were seen in patients, who had consumed large quantities of alkalis for several years for relief of pain from gastric or duodenal ulcers. This incidence is high and must be considered as a possible cause of the tubular defect. The constantly basic urine may have altered the ionic exchange between hydrogen and sodium ions in the tubular cells.

CONCLUSION

It seems imposible at present to make a clear-cut description of salt-losing nephritis. The etiological factors are indefinite and the exact mechanism of the impaired tubular reabsorption of sodium is obscure. The clinical picture is rather well defined, and the adequate treatment usually is followed by rapid clinical improvement.

The recognition of this abnormality and further investigations of the electrolyte pattern and the sodium excretion in patients with chronic renal diseases are needed before the true nature of the disease is identified.

SUMMARY

One new case of salt-losing nephritis is added to the 13 cases already published. This patient had a previous history of renal disease and calcifications in both kidneys. His daily output of sodium in the urine avaraged 470 meq per 24 hours. He responded well to treatment with a high-sodium diet + 15 gms of NaCl in tablets daily. The literature of the 13 published cases is briefly reviewed.

References:

1) *Borst, J. R.:* Acta Med. Scand. 1949, *136:* 1.
2) *Cheyne, A. I. & T. P. Whitehead:* The Lancet 1954, *266:* 550.
3) *de la Balza, F. A. & A. Onativa:* Med. B. Aires 1947, *7:* 60 (cit. 5).
4) *Enticknap, J. B.:* The Lancet 1952, *263:* 458.
5) *Joiner, C. L. & M. G. Thorne:* The Lancet 1952, *263:* 454.
6) *Murphey, F. D., A. L. Settini & N. J. Kozokoff:* Ann. Int. Med. 1953, *38:* 1160.
7) *Nussbaum, H. E. & W. G. Bernhard:* New Engl. J. Med. 1952, *246:* 289.
8) *Rosenheim, M. L.:* The Lancet 1951, *261:* 505.
9) *Sawyer, W. H. & C. Solez:* New Engl. J. Med. 1949, *240:* 210.
10) *Svensgaard, E.:* Hosp.tidende 1934, *77:* 977.
11) *Thorn, G. W., G. F. Koepf & M. Clinton:* New Engl. J. Med. 1944, *231:* 76.

LATENT SYPHILIS IGNORÉE AND SYPHILIS CONTROL DURING THE EPIDEMIC IN DENMARK 1942 — 1949

WITH AN ANALYSIS OF AGE DISTRIBUTION

By INGE BORUP SVENDSEN

In a paper in this issue of Danish Medical Bulletin Alice Reyn has given a brief description of the Syphilis Index at Statens Seruminstitut in Copenhagen and listed a number of studies which have been greatly faciliated by the Index in collecting the patient material. Many of these studies could not have been carried out, if the Index had not existed.

This applies also to the study to be reported in abstract below. For more detailed information the reader is referred to I. Borup Svendsen 1953 (1).

Gradually as the great syphilis epidemic of the forties has subsided and fresh cases have again become rare — at least in Denmark — the predominant cases are those diagnosed on the basis of a consistent, strongly positive seroreaction without clinical evidence of syphilis (latent syphilis ignorée). As a rule, the positive seroreaction is detected in a routine blood specimen.

A few years ago, P. Krag, Head of the Serodiagnostic Department of Statens Seruminstitut, suggested to me a study of the frequency with which such latent cases were detected in routine blood specimens, as this frequency might give an idea of the prevalence of unrecognized, seropositive syphilis. Of course it had to be realized that even consistent, positive reactions might be nonspecific, that the prevalence of latent seropositive syphilis could not be expected to be quite the same in all social classes, and that the material available was chiefly derived from hospitals.

The present study consists in a comparison of the prevalence of »latent syphilis ignorée« before and after the second world war. It might be imagined that the epidemic had entailed an increase in this rate, but this need not be so, if only the measures to meet the epidemic have been sufficiently effective.

One means of combating the epidemic and its consequences was the great increase in the number of blood specimens sent in for serological testing.

This increase was due in part to the increased number of control blood specimens due to the numerous new cases of syphilis and in part to the increased practice of routinely sending in blood specimens.

Despite this marked increase in the number of blood specimens, the absolute number of cases of latent syphilis ignorée detected in 1949 is only slightly higher than that found in 1939. This may be seen in Table I giving the values from the monthly lists from 1938—1949 inclusive (cf. Alice Reyn's paper).

For comparison, Table I gives the number of fresh, clinically manifest cases which as late as in 1949 was about twice that in 1938—39.

In the monthly list, latent syphilis ignorée (not previously diagnosed cases) comprises 3 groups (cf. Table I) of which most interest attaches to

Table I.

Table I. *Previously unreported cases of syphilis registered 1938 to 1949.*

A. Males

Year	Total Syphilis	Primary	Secondary	Total P and S	Latent with history	Latent with consistent reaction	Latent without history	Total latent
1938	434	187	104	291	42	5	96	143
1939	519	222	94	316	63	9	131	203
1040	477	177	126	303	52	2	120	174
1941	469	218	87	305	38	13	113	164
1942	686	276	181	457	78	5	146	229
1943	1611	989	338	1327	104	6	174	284
1944	2363	1636	345	1981	165	5	212	382
1945	2485	1631	426	2057	183	12	233	428
1946	2355	1512	446	1958	177	13	207	397
1947	1519	948	205	1153	109	12	245	366
1948	1205	698	181	879	99	31	196	326
1949	787	407	124	531	76	24	156	256

B. Females

Year	Total syphilis	Primary	Secondary	Total P and S	Latent with history	Latent with consistent reaction	Latent without history	Total latent
1938	385	47	113	160	85	3	137	225
1939	438	46	110	156	106	6	170	282
1940	413	40	116	156	85	6	166	257
1941	511	65	159	224	97	3	187	287
1942	811	78	244	322	194	5	290	489
1943	1579	316	689	1005	333	2	239	574
1944	2412	550	1060	1610	474	13	315	802
1945	2464	490	1162	1652	456	16	340	812
1946	2191	468	1043	1511	381	10	289	680
1947	1386	290	493	783	237	19	347	603
1948	1052	178	355	533	200	22	297	519
1949	669	140	215	355	86	23	205	314

From Statens Seruminstitut, Copenhagen.
Chief: *J. Ørskov.*

Table II.

Elimination of nonroutine blood tests from total blood tests by means of a sample distribution.

Findings of random sample	April 1, 1939 to April 1, 1940		May 1, 1949 to May 1, 1950	
Total in sample	402		415	
Children under 15 years of age	19		16	
Foreigners	0		5	
Donors	85		27	
Pregnant women	(no inf.)		74	
Spinal fluids	13		4	
Previously recorded cases	80		48	
Dept. of Dermatology, etc.	9		27	
Not to be classified	—		1	
To be eliminated	206		202	
Routine tests (remainder "R")*)		196		213
Per cent routine		*49*		*51*
Number of routine tests (male)		79		90
Per cent of routine tests (male)		40,3		42,2

Application to total blood tests.

Total blood tests	160,849		414,789	
Times per cent routine (sample)	*49*		*51*	
Total routine blood tests	78,400		213,000	
Times per cent male (sample)	*40,3*		*42,2*	
Total routine male blood tests		31,600		90,000
Total routine female blood tests		46,800		123,000

*) "R" indicates those physicians and departments that are presumed to send in blood tests as a matter of routine, i. e., medical and surgical departments, general hospitals, special departments (except dermatological), etc.

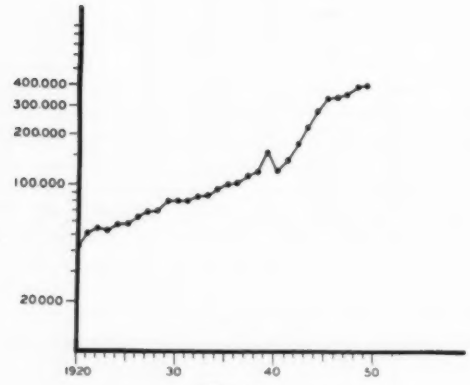


Fig. 1.

Number of blood tests sent to Statens Seruminstitut for serodiagnostic examination for syphilis per annum (from April 1 to April 1) from 1920 to 1950.

the latent cases without a history), detected by accidental, routine serologic tests.*

For the period April 1, 1939 to April 1, 1940 the author took as random samples each 400th card accompanying the blood specimens and among them selected those that were assumed to have been sent in routinely (int. al. by excluding specimens sent in by dermato-venereologists or derived from foreigners, previously registered patients (control tests, etc.)). In the same way, every 1000th card for the period May 1, 1949 to May 1, 1950 was picked out and the »routine« ones selected.

This was followed by a perusal of the latent cases on the monthly lists without a history.

The final result of the study is set out in Table IV.

It is evident from Table IV that from 1939 to 1949 there has been a statistically significant decrease in the number of cases of latent syphilis ignorée detected per 1000 blood specimens.

Thus, despite the recent epidemic, there do not seem to be more undetected cases of latent syphilis ignorée than prior to the epidemic — at least judging by the routine blood specimens sent to Statens Seruminstitut. The measures instituted to combat the epidemic must, therefore, be considered rather satisfactory in detecting the greatest possible number of infected persons as early as possible.

*) Latent with history is taken to mean e. g. the information that the spouse is suffering from syphilis, that the patient has had gonorrhoea or sores on the genitals, etc.

AGE DISTRIBUTION IN LATENT SYPHILIS IGNORÉE

It was mentioned in the paper abstracted above that the age distribution had been analysed in

Table III.

Group	April 1, 1939 to April 1, 1940				May 1, 1949 til May 1, 1950			
	Males		Females		Males		Females	
	9	8	9	8	9	8	9	8
Total	151	8	171	4	154	24	211	26
Children under 15 years	3		1		2		1	1
Foreigners	3		1		4		1	
Donors	18	7	22		8	1	5	3
Pregnant women			no information				43	3
Departments of Dermatology and Venereology, etc.	5		8	1	25	11	14	3
Remainder (i. e. uncorr. "R")	122		139		115		147	
a. Transferred following revision to other groups of the monthly list	11		12		5	4	12	3
b. Nonspecific	18		24	1	23	2	21	2
c. Only one test without information regarding disease, often accompanied by nonspecific reaction	11		14	2	14	3	6	5
d. No clinical signs of syphilis and no history obtained	45	93	61	101	7	86 1	20	114 4
e. Latent cases of syphilis with a negative history	37		26		65		88	
f. Cannot be classified according to the above-mentioned criteria			2		1			
Remaining in Group "8" of the monthly list within "R"		1				2		2
Maximum number of latent cases of syphilis ignorée (c + d + e + max. number of latent cases from Group 8)	93 + 1 = 94		101 + 2 = 103		86 + 6 = 92		114+11=125	

Distribution of all cases of latent *syphilis ignoree* with a negative history recorded for the first time (Group 9 of the monthly list) during the periods April 1, 1939 to April 1, 1940 and May 1, 1949 to May 1, 1950. In addition, to the right in each column, Group 8 of the monthly list (specimens with strong positive reaction, but no history obtained) distributed in the same manner.

Table IV.

April 1, 1939 to April 1, 1940.

	Males	Females	Males + Females
Maximum number of latent cases	$\frac{94}{31,600}$ = 3.0 per thous.	$\frac{103}{46,800}$ = 2.2 per thous.	$\frac{197}{78,400}$ = 2.5 per thous.

May 1, 1949 to May 1, 1950.

	Males	Females	Males + Females
Maximum number of latent cases	$\frac{92}{90,000}$ = 1.0 per thous.	$\frac{125}{123,000}$ = 1.0 per thous.	$\frac{217}{213,000}$ = 1.0 per thous.

Calculation of the detection rate of latent syphilis ignorée on the basis of the number of newly discovered latent cases of Group "9," "R," and the number of blood tests sent in to Statens Seruminstitut for serodiagnostic examination for syphilis corresponding to Group "R" (cf. Tables II and III).

some detail and that the result would be published later.

Originally, the concepts »maximum« and »minimum« detection rate of latent syphilis ignorée were set up. In the statistical analysis of the age distribution to be reported below only the »maximum« rate was used, because it was considered more reliable.

A total of 402 random samples were picked out from all the blood specimens sent in during 1939. Out of these 402, 195 represented routine specimens, viz. 79 from males and 116 from females. For the year 1949, 415 random samples were taken; of these 213 were routine specimens, 90 from males and 123 from females.

It was investigated how many cases of latent syphilis ignorée detected by routine blood tests were included in the groups from these two years. In 1939 the number was 94 males and 103 females, and in 1949 92 males and 125 females.

As mentioned (Table IV), the cases of latent syphilis ignorée not previously diagnosed were

in 1939 3 per thousand males and 2.2 per thousand females, whereas the corresponding value in 1949 was 1 per thousand for both sexes. Table V a and b gives a survey of the incidence of latent syphilis ignorée in 15-year age groups, a calculation of the incidence in 5-year age groups having shown only a negligible difference between three 5-year groups.

Table V a.

Incidence of newly detected latent syphilis ignorée in 15-year age groups.

April I, 1939 to April 1, 1940.

Males	Age	Number of random samples (n_i)	Number of cases with latent syphilis ignorée (a_i)	Estimate of incidence (I_i per thous.)	Standard error of I_i
N	15—29	13	7	1.3	0.61
— = 400	30—44	23	30	3.3	0.83
n	45—59	24	26	2.7	0.70
	60—74	15	25	4.2	1.28
	≧75	4	6	3.8	2.38
	Total:	79(n)	94(a)	3.0	
Females					
N	15—29	45	19	1.1	0.27
— = 400	30—44	37	30	2.0	0.46
n	45—59	13	31	6.0	1.89
	60—74	19	16	2.1	0.69
	≧75	2	7	8.8	6.79
	Total:	116(n)	103(a)	2.2	

Table V b.

Incidence of newly detected latent syphilis ignorée in 15-year age groups.

May 1, 1949 to May 1, 1950.

Males	Age	Number of random samples (n_i)	Number of cases with latent syphilis ignorée (a_i)	Estimate of incidence (I_i per thous.)	Standard error of I_i
N	15—29	26	6	0.2	0.10
— = 1000					
n	30—44	27	13	0.5	0.15
	45—59	22	36	1.6	0.41
	60—74	12	27	2.3	0.74
	≧75	3	10	3.3	2.17
	Total:	90(n)	92(a)	1.0	
Females					
N					
— = 1000	15—29	46	33	0.7	0.15
n	30—44	36	29	0.8	0.19
	45—59	27	28	1.0	0.26
	60—74	10	28	2.8	1.00
	≧75	4	7	1.8	1.09
	Total:	123(n)	125(a)	1.0	

The procedure in the investigation of age distribution in latent syphilis ignorée was as follows*):

*) Mr. Michael Weis Bentzon, actuary, has kindly derived the expressions for the standard errors.

The number of routine blood specimens found by taking random samples is called n and the corresponding number of blood specimens N (these values are e. g. for males 1939 = 79 and 31.600, every 400th card from 1939 being taken as a random sample).

The random cases comprise n patients of all ages from 15 years, i. e. $n = n_1 + n_2 \ldots\ldots, n_1, n_2, n_3$ etc. being the number of specimens in the various age groups.

Among the N recorded specimens there were a with latent syphilis ignorée, a_i being in the i'th age group ($a_1 + a_2 + \ldots = a$). The estimate (I) of the incidence in a given age group is calculated by the formula:

$$I_i = \frac{a_i}{N\frac{n_i}{n}} = \frac{a_i}{n_i\frac{N}{n}}$$

The variance of the estimate is determined by the approximation formula

$$V\{I_i\} \simeq I_i^2 \left(\frac{1}{a_i} + \frac{1 - \frac{n_i}{n}}{n_i}\right)$$

(This approximation is valid only when a_i and n_i are not too close to 0).

In comparing the incidence for two age groups, "i" and "j", regard must be paid to the fact that the estimates I_i and I_j are dependent on each other. That is

$$V\{I_i - I_j\} = V\{I_i\} + V\{I_i\} - 2V\{I_i, I_j\}$$

$$\simeq I_i^2 \left(\frac{1}{a_i} + \frac{1 - \frac{n_i}{n}}{n_i}\right) + I_j^2 \left(\frac{1}{a_j} + \frac{1 - \frac{n_i}{n}}{n_j}\right) +$$

$$2\left(\frac{1}{N} + \frac{1}{n}\right) I_i \; I_j$$

As apparent from the tables it is justified to consider the incidence per age group the same for males and females in 1939, the difference not exceeding twice the standard error in any case. Example: Age group 45—59 for males and females respectively in 1939:

$$6.0 - 2.7 = 3.3. \text{ St. error} = \sqrt{0.70^2 + 1.92^2} = 2.1$$

In 1949 there was a significantly smaller number of males than of females in the youngest age group (15—29 years), but in the other age groups there was no such difference.

This difference in the youngest age group accords well with the fact that it is more difficult to diagnose fresh syphilis in females than in males. Since, moreover, the majority of cases infected during the epidemic were from the younger age groups, it is not surprising to find among the

females a "remainder" of cases not detected until by routine blood test in the latent stage.

Furthermore, it will be seen from Table V a and b that in 1939 as well as in 1949 both males and females show a tendency to increasing incidence of syphilis ignorée with advancing age. To investigate this more closely, males and females were considered as one group for 1939 and for 1949 respectively (Tables VI), the youngest age group in 1949 being left out because it showed a significant difference between males and females.

Table VI shows, as might be expected, that the incidence of syphilis ignorée increases with advancing age. It is emphasized, however, that in the oldest age groups the standard error is very high because of the small number of random samples taken (n_i).

Table VI.

Incidence of newly detected latent syphilis ignorée in 15-year age groups (males + females).

April 1, 1939 to April 1, 1940.

Age	Number of random samples (n_i)	Number of cases with latent syphilis ignorée (a_i)	Estimate of incidence (I_i per thous.)	Standard error of I_i
15—29	58	26	1.1	0.25
30—44	60	60	2.5	0.42
45—59	37	57	3.9	0.76
60—74	34	41	3.0	0.67
≥75	6	13	5.4	2.65
Total:	195(n)	197(a)	2.5	

May 1, 1949 to May 1, 1950.

15—29	72	39	0.5	0.10
30—44	63	42	0.7	0.12
45—59	49	64	1.3	0.23
60—74	22	55	2.5	0.61
≥75	7	17	2.4	1.08
Total:	213(n)	217(a)	1.0	

The incidence of latent syphilis ignorée is in all age groups lower in 1949 than in 1939. This difference is significant for the age groups 30—44 and 45—59 years.

It must be assumed that the majority of cases infected during the epidemic in 1942—1949 were of the younger age groups. A presumed remainder of undetected cases would probably manifest itself as an increase in latent syphilis ignorée in the younger age groups, but as already mentioned this is not so. This finding gives further support to the assumption that the measures instituted to combat the epidemic were fairly satisfactory, so that the majority of the infected cases were diagnosed shortly after the infection.

Acknowledgment. — For valuable assistance in carrying out this study I am indebted to Drs. *P. Krag, A. Reyn,* and *E. Ellehøj* of Statens Seruminstitut.

Reference:

Borup Svendsen, I.: Am. J. Syph. Gon. Ven. Dis. 1953, *37:* 553—573.

THE SYPHILIS INDEX AT STATENS SERUMINSTITUT, COPENHAGEN

By ALICE REYN

In Denmark, serological testing for syphilis is centralized at the Serodiagnostic Department, Statens Seruminstitut. Serological testing for syphilis is widely used throughout the whole country; nearly all patients admitted to the larger hospitals in Copenhagen and to most of the larger provincial hospitals are checked for syphilis as a matter of routine. Practitioners also are using serological testing for syphilis to a wide extent.

Syphilis Index.

The Index covers the whole of Denmark. In the great majority of cases the patients are identified by means of sex, first letter of surname(s), exact date of birth, name of physician (or hospital) diagnosing the cases, and date of diagnosis, the idea being to register the patients anonymously. Information on the identification marks is obtained from forms accompanying the blood samples.

The idea to build up an anonymous index was suggested in 1919 by J e r s i l d, chief of the Rudolph Berghs Hospital in Copenhagen, and the Index was established in April, 1920. It is beyond doubt the only one of its kind in the world.

All physicians (in private practice or attached to hospitals) can obtain copies of their patients' index cards containing the results of all tests performed since 1920, and they can get the names of previous doctors consulted, hospitals attended etc. Another main object is to afford statistics and to facilitate scientific investigation on syphilis.

If the accompanying forms of the blood samples contain no particulars of present or previous

From Statens Seruminstitut, Copenhagen.
Chief: *J. Ørskov.*

syphilis, and the laboratory reports are positive or doubtful, the index is consulted by the laboratory staff. In cases of possible identity, copies of the index cards are sent together with the report on the laboratory results and in case of non-identity the copies are returned to the Index. Negative specimens without any information about syphilis are not checked against the Index — if not requested — until the final registration takes place, i. e. from 3—6 weeks after the samples have been received. Samples from pregnant women form an exception from this rule so that irrespective of the serological results they are all checked against the Index, and copies accompanied by special forms are sent to the doctors together with the reports on serological testing.

In all cases not previously registered special forms are sent out with the serological report, when the forms forwarded with the blood samples contain no information about clinical symptoms. Supplementary questionnaires are sent out later if the diagnosis cannot be settled at the time when the answers are sent out.

On 1. 1. 1954, the Index contained about 185.000 cards. It includes not only all the syphilitics (seronegative and seropositive) from whom blood samples have been sent in since 1920*), but also a certain number of patients with presumably non-specific seroreactions. Annual mortality lists are obtained from the National Health Service, so that the cards of dead syphilitics can be removed from the index.

All particulars of clinical findings are noted on the cards and all patients not previously registered are classified into mainly clinical groups forming the so-called »monthly list« (Peter Krag 1936). These lists provide statistical information as to changes in the distribution of the new cases in primary, secondary, tertiary, congenital and latent syphilis etc.

The Syphilis Index has played an important role in a long series of scientific publications on the diagnosis, treatment, prognosis and epidemiology of syphilis. The evaluation of recent serological methods (use of cardiolipin antigen and the T. P. I. test) has been highly facilitated by information obtainable from the Index.

Notification of Syphilis.

Acquired and congenital syphilis have been notifiable to the National Health Service since 1877.

Since 1938 the following particulars have been added to the weekly notification lists sent in to the National Health Service: the names of practitioners notifying fresh, acquired syphilis and, since 1942, the sex, initials, date of birth and case-book number of the patients. Copies of the notification lists are forwarded to the Syphilis Index of the Statens Seruminstitut, as soon as they are received from the practitioners and health officers. The patients on the lists are checked against the patients entered in the index.

Thus, seronegative cases (mainly primary syphilis) without information on the corresponding forms, and cases in which no blood tests have been sent as yet, are entered into the index. The »false« notifications i. e. duplicate notifications and patients with old syphilis, are removed from the official notification lists.

*) Since 1940 supplemented with a small number of cases in which no samples at all have been sent in.

LIST OF SCIENTIFIC PUBLICATIONS

A. Papers in which further information on the Index can be found.

Th. Madsen & P. Krag: Syphilitic Registration Office of the State Serum Institute. Acta derm.-ven. 1937, *18:* Fasc. 4, 546.

P. Krag: Medical Organization in Denmark. Brit. med. Journ. 1947, *2:* 10.

A. Kissmeyer: The Combating of Venereal Diseases in Denmark. The National Health Service, 1938. 2nd Edition 1949.

A. Reyn: The Combating of Venereal Diseases in Denmark with special Reference to the Tests Performed at the Statens Seruminstitut, Copenhagen. Calcutta Medical Review. In print.

B. Papers using information from the Syphilis Index, published by the Statens Seruminstitut, Copenhagen.

P. Krag: Forbigående (uspecifik) stærk Wassermann-Kahn-Reaktion, U. f. L. 1936, *98:* 855.

P. Krag & A. Lønberg: 53 tilfælde af forbigående (uspecifik) stærk Wassermann-Kahn-Reaktion. U. f. L. 1938, *100:* 497.

P. Krag & A. Lønberg: The Occurrence of Strong Unspecific Wassermann-Kahn-Reaction. Acta derm.-ven. 1938, *19:* Fasc. 6, 612.

P. Krag: Sensitiveness and Specificity of a Bordet-Wassermann Reaction (Moorch) and Kahn's Standard Reaction. Bull. of the Health Organizat. of the League of Nations. 1938, *7:* Extr. 7, 451.

P. Krag & M. Lindhardt: Syfilisstatistik. U. f. L. 1939, *101:* 1495.

A. Reyn: Specifike og uspecifike Syfilisreaktioner og deres Forløb. U. f. L. 1941, *103:* 137.

A. Reyn: »Familiær« Optræden af uspecifik, positiv Wassermann-Kahn-Reaktion. U. f. L. 1941, *103:* 145.

P. Krag: En Undersøgelse over Dødelighed og Syfilis. U. f. L. 1941, *103:* 1077.

P. Krag & M. Lindhardt: Syfilisstatistik. Anmeldelse af frisk Syfilis på Ugelisterne i 1940. U. f. L. 1942, *104:* 560.

O. Bang & P. Krag: Serodiagnosen af Syfilis hos medicinske Patienter. U. f. L. 1943, *105:* 273.

P. Krag, M. Lindhardt & O. Maaløe: Syfilisstatistik. Anmeldelse af frisk Syfilis på Ugelisterne 1942. U. f. L. 1943, *105:* 1252.

P. Krag & M. Lindhardt: Syfilisstatistik. Anmeldelse af Syfilis congenita i Årene 1940—42. U. f. L. 1944, *106:* 528.

P. Krag & E. Dalsgaard-Nielsen: Studies on Congenital Syphilis Diagnosed in the Period of 1935—39. Acta path. et microbiol. scand. 1944, *21:* Fasc. 2, 264.

O. Maaløe: Om de sjældne sero-negative Tilfælde af sekundær Syfilis. U. f. L. 1945, *107:* 1108.

P. Krag & J. Røjel: Wassermann-Reaktionen hos gravide. U. f. L. 1947, *109:* 493.

P. Wiingaard: Den fortsatte observation og kontrol med syfilitikere i Danmark. U. f. L. 1947, *109:* 557.

P. Wiingaard: »Uspecifike« (paraluiske) seroreaktioner og de lidelser, specielt luftvejslidelser, der knytter sig hertil. With an English Summary. Thesis, Copenhagen 1948. Rosenkilde og Bagger's Forlag.

P. Wiingaard: WR-undersøgelsen af de gravide. U. f. L. U. f. L. 1949, *111:* 600.

O. Nørgaard: Investigation into Strong Anticomplementary Human Sera. I & II. Acta path. et microbiol. scand. 1950, *27:* Fasc. 6, 811.

O. Nørgaard: La réaction de Wassermann sur le sang du cordon ombilical. Acta derm.-ven. 1951, *31:* 153.

A. Reyn & H. Schmidt: Cardiolipin. Et nyt antigen til anvendelse ved serodiagnosen af syfilis. U. f. L. 1951, *113:* 1427.

H. Schmidt: Cardiolipin Antigen. I. A Qualitative Examination of Sensitivity and Specificity. Brit. Journ. of Ven. Dis. 1951, *27:* 23.

H. Schmidt & A. Reyn: Sammenligning mellem »urenset« oksehjerte-antigen (Modifikation Mørch 1933) og cardiolipin-antigen anvendt til serodiagnosen af syfilis. U. f. L. 1952, *114:* 1485.

H. Aa. Nielsen & A. Reyn: En ny serodiagnostisk prøve for syfilis: T. P. I. (Nelson). U. f. L. 1952, *114:* 1477.

A. Reyn & H. Aa. Nielsen: Preliminary Results in the Treponemal Immobilization Test (Nelson). Acta derm.-ven. 1952, *32:* Suppl. 29, 303—15.

I. Borup Svendsen: Age and Sex Distribution of Patients with Fresh Syphilis. Acta derm.-ven. 1952, *32:* Supp. 29, 353—59.

H. Schmidt: Cardiolipin Antigen. II. A Quantitative Examination of Sensitivity. Brit. Journ. of Ven. Dis. 1952, *28:* No. 4, 169.

H. Schmidt: Cardiolipin Antigen. III. An Examination of Specificity. Brit. Journ. of Ven. Dis. 1953, *29:* No. 2, 84.

I. Borup Svendsen: Latent Syphilis Ignorée and Syphilis Control during the Epidemic in Denmark 1942 to 1949. Am. Journ. of Syph. Gon. & Ven. Dis. St. Louis. 1953, *37:* No. 6, 553—73.

J. Røjel: The Interrelation Between Uterine Cancer and Syphilis. A Patho-demographic Study. Thesis, Copenhagen 1953. Nyt Nordisk Forlag, Arnold Busck.

H. Schmidt: Cardiolipin Antigen. IV. Incidence of Positive Sero-Reactions for Syphilis in »Normal« Persons. Acta derm.-ven. 1954, *34:* 159.

H. Schmidt & H. Lundbäck: Cardiolipin Antigen. V. Studies on the Maturation Phenomenon. Acta path. et microbiol. scand. 1954, *34:* 509.

H. Aa. Nielsen: Clinical Value of the T. P. I. Test. Acta derm.-ven. 1954, *34:* 102.

O. Nørgaard: Investigations into Strongly Anticomplementary Human Sera. III. Acta path. et microbiol. scand. 1954, *34:* Fasc. 4, 336.

P. Wiingaard: Follow-up of Presumably Insufficientiy Treated Cases of Syphilis. To be published.

H. Schmidt: Cardiolipin Anttigen VI. Examination of an Incomplete Cardiolipin Antigen I. Acta path. et microbiol. scand. In print.

H. Schmidt: Cardiolipin Antigen VII. Examination of an Incomplete Cardiolipin Antigen II. Acta path. et microbiol. scand. In print.

O. Nørgaard: Investigations into Strongly Anticomplementary Human Sera. IV. Acta path. et microbiol. scand. In print.

C. Other papers using information from the Syphilis Index.

E. Lomholt: Course of Changes in the Spinal Fluid of Syphilitics. A Clinical and Catamnestic Study. Thesis. Copenhagen 1936. Levin og Munksgaard.

E. Dalsgaard-Nielsen: Keratitis parenchymatosa luica og dens følgetilstande særligt belyst gennem sene efterundersøgelser. Thesis. Copenhagen 1938. Levin og Munksgaard.

Fr. E. Reymann: A Contribution to the Enlightenment on the Frequency of Syphilis among Workable Officers and Crews of the Danish Mercantile Marine. Acta derm.-ven. 1940, *21:* 667.

Fr. E. Reymann: Syfilis importeret til Danmark i Årene 1937—38. U. f. L. 1941, *103:* 131.

Ib Boesen: Wassermann-Reaktionens Betydning på en kirurgisk Provinsafdeling. Nord. Med. 1942, *14:* 1626.

E. Lohse: Seroreaktioner for Syfilis på en psykiatrisk Modtage-afdeling. U. f. L. 1945, *107:* 1038.

J. Aggerbeck: Cardio-vasculær lues og dens tidlige prophylaxe. En klinisk og katamnestisk studie. With an English Summary. Thesis. Copenhagen 1949. Rosenkilde og Bagger's forlag.

Poul Møller: Clinical Results and By-effects in Early Syphilis with Combined Arsenical-Bismuth Treatment. Acta derm.-ven. 1951, *31:* suppl. *24:* 30.

A. Perdrup: Penicillin versus Arsenical-Bismuth Treatment in Early Syphilis. Acta derm.-ven. 1951, *31:* suppl. *24:* 44.

K. H. Spendser: At what Stage is Syphilis Diagnosed? Acta derm.-ven. 1951, *31:* 623.

Johs. P. Nielsen: Prognostic Importance of Spinal Fluid Examination in Syphilis. A Follow-up Study of 428 Syphilitic Patients 3—37 Years after Lumbar Puncture in Latency. Acta derm.-ven. 1952, *32:* suppl. 29.

A. Perdrup, B. Heilesen and B. Sylvest: Follow-up Examination of 157 Patients with Early Mucocutaneous Syphilis Treated with Penicillin and Followed for One to Four Years. Acta derm.-ven. 1954, *34:* 133.

SUBJECT INDEX

NOTE: The Bibliographial Supplement INDEX MEDICUS DANICUS should not be bound with the DANISH MEDICAL BULLETIN, as it is paginated sepasately and will be continued independently.